THE INSTITUTE FOR THEORETICAL BIOCHEMISTRY
AND MOLECULAR BIOLOGY
P.O. Box 4512, Ithaca, NY 14852-4512

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Dr. Joshua Lederberg
1230 York Ave.
Rockefeller University
New York, New York 10021-6399

Dear Dr. Lederberg,

We were pleased to receive your note regarding our recent commentary in Nature, accompanied by several of your papers. Your theoretical paper on the antibody response was new to us, although we were aware of your interesting paper "Postmature scientific discovery" (having seen a reference to it when we read your autobiographical article in Current Contents last year). It is rare that a scientist delves beyond his/her immediate field of scientific inquiry into the philosophical and sociological matrix in which science is embedded; Peter Medawar is one of the few others to do so in recent years. We feel that scientists with "public credibility" have a particular obligation to explore and improve the social and philosophical structure of science; unfortunately, you are one of a mere handful making the attempt.

Your first question, to wit, whether the 6 year delay before Peter Mitchell's chemiosmotic hypothesis was seriously tested by other scientists was an egregious one, depends upon the probable causes for the dalay. Sometimes, such delay may be due to technical limitations; this is occasionally the case in physics (for instance, the Nobel prize given to Carlo Rubbia was for devising an ingenious method of experimental testing in high-energy physics where technical limitations had previously hindered such experiments). In other cases, a scientist may propose ideas addressing a question which is not recognized as problematic or fruitful by other researchers. An example of this type is found in the area of metabolic regulation, in which H. Kacser and colleagues proposed a new theoretical and methodological framework by which to analyze the kinetic and regulatory structure of metabolic pathways. It was 9 years before the first experimental paper using this approach was published by a group other than that of Kacser et al. The power of this new approach has only recently begun to be used more widely, since other researchers were initially reluctant to replace the existing simple (but inadequate) scheme with a more complex framework possessing more precision and explanatory power, and instead treated these new ideas with suspicion or ignored them. Essentially, Kacser and his colleagues had not only to propose new ideas, but to show that these ideas filled a need which had not previously been perceived to exist. The delay in this case was further exacerbated by the requirement that those using this new framework have an elementary understanding of algebra and calculus, which is usually sufficient to scare off most biologists.

In Mitchell's case, there was an acute recognition that the existing paradigm was not producing the expected experimental results, despite an extensive search for the putative phosphorylated intermediates proposed in then-current hypotheses of oxidative phosphorylation; researchers in the field should therefore have been sensitized to the need for alternative explanations (i.e. they should have been experiencing a Kuhnian crisis). However, even though Mitchell's hypothesis was both demarcated (containing explicit falsifiable predictions) and also explained the failure of experimentalists to find chemical "couplers" between the respiratory chain and ADP phosphorylation, most biochemists in the field were apparently reluctant to test this alternate model. In addition, new methodologies were required to carry out these experimental tests, and it was not until Mitchell and Moyle had produced a variety of quantitative methods (and data) which "imitators" could utilize that other experimentalists joined the search. Those in the field were already working on the problem of how respiration was coupled to phosphorylation, therefore a "shift in vector" should not have been difficult conceptually for them. Our interpretation of what we know of the events (which is not first-hand knowledge) is that much of the delay on the part of other researchers derived from psychological resistance to these new ideas, and lack of the experimental innovation to develop techniques needed to test these new ideas.

It is true that researchers must carefully evaluate what new ideas are worth their time so that they do not waste valuable time and resources, and this may account for some of the delay in the case of Mitchell's hypothesis and others'. However, we would classify a delay as "egregious" if the major period of the delay appears to be due largely to non-rational evaluations of the potential of a proposal.

As a comparison, one might look to areas of physics or chemistry in which theory is viewed as more integral to the field. Although we have only anecdotal data, it would appear that, in general, the delay between proposal of a testable hypothesis and testing in these fields is on the order of a few years or less (technical difficulties aside). Obviously, other factors come into play as far as the differences between fields of physics and fields of biology; but in a case where the problem set is well-defined, where practioners are actively working on that problem, and where experimental tests of existing paradigms have failed to produce the expected evidence, then one should expect that a new testable hypothesis would elicit a rapid response from the experimental community. Unfortunately, as we wrote in our commentary, most biologists are not accustomed to ideas that are presented "merely" as testable hypotheses without supporting data produced by the author(s) himself; usually the original proponent of a testable idea is also expected to do the experimental testing. One reason for this may be that biology as a whole (with a few exceptions) does not recognize that theoreticians and experimentalists usually possess different kinds of minds. The theoretician will usually do experiments because they are necessary in order to have his/her ideas seriously considered by others (although s/he will usually do the least number of the most crucial experiments, as Neils Jerne is reputed to have done), whereas the experimentalist relishes experimentation. Obviously, there is a continuum between the theoretician and the experimentalist. You are one of a small group of scientists who possess both a penchant for hypothesis and the patience and expertise for experiment, which may partly explain your own success (since you were both able to formulate new ideas and to test them).

Regarding your second question on unexplored theory in biology, we are not sure whether you refer to fields of biology which are ripe for scientific hypotheses which have not been forthcoming, or whether you are interested in hypotheses which have been proposed but not tested. We are aware of examples of both situations in our own areas of phospholipid and muscle biochemistry, metabolic regulation, and genetic/nutritional interactions.

You are undoubtedly aware that the sequence of events for a genetic disease leading from genotype to clinical phenotype is not understood for any disease affecting the nervous system (at least as far as we know). One reason for this is that there is no developed theory of <u>systems</u> in biology which includes the design and operation of control systems; details may be known at the molecular level and the histological (or anatomical) level, but ignorance of the connecting systems makes it impossible to predict the gross clinical effects of a genetic lesion, or to explain the differential expression of a common defect in different tissues and in different species. This ignorance relects the lack of integration between molecular biology, biochemistry, transmission genetics, and pathology. Nature acts as an integrated whole, but territorial views of neighboring fields will produce conceptual gaps and discourage the necessary integration of disciplines (as you have discussed for the case of sexual recombination in "Postmature scientific discovery"). New hypotheses frequently involve attempts to bridge the gap between fields, however such attempts will often be viewed as threats by practioners of a field when the new ideas impinge upon their "territory" (as discussed in Mulkay's "The Social Process of Innovation").

A classic example of the above situation is PKU, in which the genetic and enzymatic defects are fairly well characterized, but neither the actual cause(s) of mental retardation, nor the reasons for variability in mental function given similar degrees of plasma phenylalanine, are understood. Similarly, most of the explanations for vitamin deficiency manifestations are _post hoc_ explanations which do not address underlying questions of why _particular_ tissues shows _particular_ pathologies, nor do they address the well-known inter-species variability in vitamin deficiency signs. Only rarely, if at all, are such explanations presented as demarcated falsifiable hypotheses.

As another example, the mechanisms whereby "risk factors" contribute to disease processes are almost universally unknown, and much of the conventional wisdom in the nutritional management of diseases is based as much or more upon epidemiological "black boxes" and old wives' tales as upon mechanistic hypotheses which have been tested. Examples of such relationships which are not connected by demarcated hypotheses include sodium and hypertension, elevated serum cholesterol and atherosclerotic plaque formation, selenium deficiency and increased cancer risk, etc. In fact, most fields that utilize epidemiological or correlational approaches tend to substitute such correlational "black boxes" for mechanistic hypotheses (rather than using such correlations as a starting point for mechanistic research); such fields can _never_ advance beyond associations to explanations without scientific mechanistic hypotheses. Unfortunately, despite the very obvious exceptions to most such correlations (which should point out the multivariable nature of most such problems), little is usually done to encourage the proposal of mechanistic hypotheses. In fact, such exceptions are usually seen as bothersome details rather than as welcome clues that something else is going on and that new ideas are needed.

In some fields, the absence of hypothesis may be due to suppression of alternative views rather than to an absence of ideas. A powerful example of a field in which conflicting proposals have been notably repressed is the controversy over whether AIDS is truly caused by the human immunodeficiency virus, or whether another agent is responsible, or whether the disease is the outcome of several interacting factors. A recent book entitled _AIDS: The HIV Myth_ by Jad Adams (Macmillan, London, 1989) describes how many scientists involved apparently neglected a scientific approach, choosing advocacy over objectivity and silencing opposition by force or ridicule rather than reason. This is not to say that HIV may not be one of, or the only, causative agent of AIDS, but merely to point out that the field could benefit from rigorous analysis and alternative falsifiable hypotheses whose predictions would provide a way to weed out some of the more fuzzy-minded thinking in the area. Two researchers writing in response to our commentary included a copy of a demarcated hypothesis they published on the pathogenesis of AIDS (Ascher, M.S. & Sheppard, H.W. (1988) Clin. Exp. Immunol. 73, 165); they met with resistance and difficulties in publishing their ideas, even though they possess the appropriate credentials (however, being from a state Dept. of Health they may have suffered from additional sociological handicaps).

The case in which new proposals in biology remain untested generally is a subset of the broader problem of resistance to new ideas in science (a problem, which as you know, has been more thoroughly examined by Barber, Stent, Mulkay and others). This resistance can be manifested in several ways, including difficulties in publishing new ideas, difficulties in getting financial and institutional support to test such hypotheses, and difficulties in recruiting experimentalists to test such hypotheses. In addition to the above example of Kacser et al., in which it took 9 years before other experimentalists used their ideas, we can cite examples from our own experience. We have published a number of demarcated hypotheses that incorporated data which were previously unexplained by (or contradictory to) existing paradigms. One of these, (FEBS Lett. (1984) 170, 1; TIBS (1987) 12, 131), proposes new biosynthetic pathways for acyl-specific phospholipids and entails de novo synthesis of glycerophosphodiesters as the acyl acceptors, in contrast to the conventional view that these glycerophosphodiesters are purely catabolic products which are not further utilized. This new hypothesis has only recently been tested by an independent researcher (Baranska, J. (1988) FEBS Lett. 228, 175) (in addition to some experimental work done by JPI, Med. Biol. (1985) 63, 81; FEBS Lett. (1987) 214, 149). The problem of acyl-specificity of phospholipids is not just an "academic" one, since acyl-specific phospholipids represent the highest mass of lipids in cerebral cortex tissue, and constitute a significant fraction of lipids in other tissues such as muscle, retina and testes. We believe, based on available data, that these phospholipids play crucial roles in differentiation and function, and that defects in their synthesis and metabolism may be responsible for a number of presently-unexplained diseases in muscle and nervous tissue; in addition, available data indicate that derangements in glycerophosphodiester synthesis or metabolism are primary or early events in carcinogenesis. The source of acyl-specificity in phospholipids is widely recognized to be problematic, even after almost half a century of detailed data production, in that none of the previous schemes has been shown to satisfactorily account for this specificity; however, the prevailing sentiment is that existing schemes must somehow account for it, even though evidence inconsistent with accepted paradigms has been accumulating for more than 40 years and continues to appear. Since most of the researchers (mostly data producers) in this area do not attempt to deal conceptually with the problem, they have been slow to test this alternative hypothesis, despite the fact that the methodology has been published along with supporting data. We have had this scenario repeated with a number of other demarcated hypotheses, including one related to the possible role of acyl-specific phospholipids in muscle function and muscular dystrophy (J. Theor. Biol. (1985) 116, 65; Mol. Cell. Biochem. (1988) 81, 103) and one proposing co-enzyme roles for vitamin E and selenium in fatty acid desaturation (Mol. Cell. Biochem. (1986) 69, 93). We have also received correspondence from some other researchers whose ideas have been treated with determined disbelief (rather than the objective and reasoned skepticism which is the putative hallmark of the scientist) or "loud silence" (meaning the studied avoidance of new proposals which might disturb the status quo).

Obviously, all of biology is not dismal or devoid of integrity. However, our experience has been that less than 10% of the people we've dealt with (as editors, reviewers, or experimentalists) are capable, rational, and open-minded in evaluating ideas. And, unfortunately, we do not see the situation getting any better; if anything, it is getting worse, as technology and emphasis on a "just the facts" mentality slowly squeeze out those whose interest is in ideas and exploring new frontiers (not just getting finer details of previously-defined areas). Our comments are not made in a spirit of sour grapes, and concur with many other sociological and historical analyses of science; rather, we hope that by expanding opportunities for theoreticians, and by encouraging closer cooperation between them and experimentalists, many areas of biology could become both more productive and more exciting. In addition, on pragmatic grounds alone, such cooperation would undoubtedly increase the "intellectual efficiency" of federal funds allocated for research in the biological sciences. For these reasons, and because of the lack of institutional encouragement to do theoretical work, we founded the Institute last year, which we believe is the first of its kind for biochemistry and molecular biology (an idea which may be considered as crazy as founding an institute for theoretical physics would have been in 1900). Although presently small in size and budget, we hope it will be a nucleus from which will grow broader visions.

As regards your last question about whether Peter Mitchell had any difficulty in publishing his hypothesis in Nature, we do not know. However, we have met with a great deal of non-rational resistance in our attempts to publish hypotheses, and we have heard similar stories from a number of other researchers; one researcher had so much difficulty that he eventually had to resort to private publication of his ideas at his own expense (one wonders how many potential theoreticians in biology have never published as a result of such discouragement). In the same vein, we would like to know whether you had any difficulties in publishing your own theoretical work in immunology, which you describe as "pure hypothesis," and any other difficulties you had in having new ideas considered seriously or tested. Your published historical accounts emphasize the positive and supportive associations you experienced, but we would be interested in evidences of other sociological processes at work in the acceptance or rejection of your work. The idea of science and scientists as being purely rational and open-minded is a convenient fiction, but does not appear to be true in many (or most) cases of which we are aware. We would appreciate any insight you might have from your own experiences on positive and negative sociological aspects of science. The sociology of science is a field with many fruitful areas open for investigation. Perhaps in the not-too-distant future more scientists, sociologists and philosophers of science will join forces to improve upon how biology is practised.

Our purposes in writing our commentary to Nature were to increase awareness of the need for theoretical endeavors in biology, and also to stimulate correspondence to Nature (and other journals) on this subject. If you would care to share your experiences or opinions regarding opportunity (or lack of) for theoretical work in biology, we encourage you to consider writing a letter to Nature in response to our commentary. Personally, we feel the time has come for theorists in biology to "legitimize" their activities, so that formulation of testable, grounded ideas becomes a respected and more readily publishable endeavor.

Yours sincerely,

Virginia A Huszagh

Virginia Huszagh

Juan P. Infante

Juan Infante